Disclosure Statement and cited references. If the Office cannot locate these references, then Applicant will resubmit them.

A further Supplemental Information Disclosure Statement and cited references are enclosed.

REJECTION OF CLAIMS 1-64, 69-83, 87-89, 99-112 AND 117-119 UNDER 35 U.S.C. §103(a)

The Office Action has maintained the rejection of claims 1-64, 69-83, 87-89, 99-112 and 117-119 under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2)*:303-322) and the PDR (Physician's Desk Reference) entry for FLOVENT®. Applicant respectfully traverses this rejection.

The relevant law

[I]n order to establish a *prima facie* case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

Th instant claims

Instant claim 1 is directed to a pharmaceutical composition, containing

(i) formoterol, or a derivative thereof; and

(ii) a steroidal anti-inflammatory agent, or a derivative thereof;

in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Claims 2-64, 69-77 and 99-108 further describe the pharmaceutical composition of claim 1.

Claim 78 is directed to a kit, containing:

(a) an aqueous composition containing

(i) formoterol or a derivative thereof, and

(ii) a steroidal anti-inflammatory agent or a derivative thereof, formulated for single dosage administration; and

(b) a nebulizer.

Claims 79 and 80, 109, 110 further describe the kit of claim 78.

Claim 81 is directed to a combination containing;

(a) the pharmaceutical composition of claim 1 formulated for single dosage administration; and

(b) a vial.

Claims 82, 83, 111 and 112 further describe the combination of claim 81.

Claim 87-89 are directed to articles of manufacture containing the compositions of claims 1, 73 and 74, respectively.

Claim 117 is directed to a combination, containing:

a composition containing formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long

term storage, the fluid contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof; and

a composition containing a bronchodilating steroid, or a derivative thereof.

Claims 118-119 further describe the combination of claim 117.

The teachings of Hochrainer *et al.*

"Active Substance Concentrate"

Hochrainer *et al.* teaches an "active substance concentrate" containing formoterol in the form of its free base or in the form of one of the pharmacologically acceptable salts or addition products (adducts) thereof as the active substance. This "active substance concentrate" is taught as a "highly concentrated" solution or suspension (*i.e.*, greater than 10 mg/mL, preferably 75 to 500 mg/mL) that is stable for a period of several months, possibly up to several years without any deterioration in the pharmaceutical quality (see, *e.g.*, column 1, lines 55-61; column 2, lines 4-7; and claim 1).

Hochrainer *et al.* teaches that it is the high concentration that allows for the stability of the concentrate. The cited reference does not teach or suggest stable, aqueous compositions containing formoterol formulated at a concentration for direct administration to a subject in need thereof.

composition claims unclaimed limitation not

The "highly concentrated" "active substance concentrate" of the reference is not suitable for direct administration to a subject in need thereof, nor is it formulated for single dosage administration. See, *e.g.*, column 2, lines 1-4:

> The term "highly concentrated" means a concentration of the active substance which is usually too high to enable the corresponding solution or suspension to be used therapeutically for inhalation without being diluted.

See also, *e.g.*, column 1, lines 47-52:

> The active substance concentrate according to the invention may be converted, by diluting with a pharmacologically acceptable liquid which optionally contains pharmaceutical adjuvants and additives, into a

> pharmaceutical preparation (aerosol formulation) which is converted by means of a nebulizer into an inhalable aerosol.

See also, *e.g.*, column 4, lines 9-13:

> The active substance concentrate according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation. As already explained, use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation).

Thus, the "active substance concentrate" of Hochrainer *et al.* is merely a means for the storage of highly concentrated solutions of formoterol, and is not formulated at a concentration for direct administration to a subject in need thereof.

"Pharmaceutical Preparation"

Hochrainer *et al.* teaches that the "active substance concentrate" is converted to a "pharmaceutical preparation" prior to administration to a patient. See, *e.g.*, column 1, lines 47-53 and columns 4-5. The reference does not teach or suggest that the "pharmaceutical preparation" is stable during long term storage. As described in detail below, the reference teaches that such formoterol compositions are not stable during long term storage, and thus teaches away from the subject matter of the instant claims.

The "pharmaceutical preparation" of Hochrainer *et al.* is taught for administration to a patient. See, *e.g.*, column 4, lines 13-18:

> The term "pharmaceutical preparation" denotes a formulation of a pharmaceutical substance suitable for inhalation wherein a pharmaceutical substance or mixture of substances can be administered in the required and/or recommended concentration.

The reference also teaches methods for administration of the "pharmaceutical preparation" to a patient in need thereof (see, *e.g.*, columns 4-5). However, the reference does not teach or suggest that the "pharmaceutical preparation" is stable during long term storage. As described in detail below, Hochrainer *et al.* teaches away from the subject matter of the instant claims.

Hochrainer *et al.* further distinguishes the "active substance concentrate" taught therein from a "pharmaceutical preparation" at column 5, lines 16-19:

> Neither the active substance concentrate suitable for storage according to the invention nor the pharmaceutical preparation for administration obtained by dilution contains a propellant.

Differences from the instant claims

Hochrainer *et al.* teaches a highly concentrated solution or suspension of formoterol "active substance concentrate" that is suitable for storage, but is not suitable for direct administration to a subject in need thereof. The reference teaches that the formoterol "active substance concentrate" is converted to a "pharmaceutical preparation" which is administered to a patient. The reference does not teach or suggest that the "pharmaceutical preparation" is stable during long term storage.

In contrast, the pharmaceutical compositions of the instant claims, containing formoterol and a steroidal anti-inflammatory agent or derivatives thereof, are formulated in a pharmacologically suitable fluid, where the composition is stable during long term storage, the fluid contains water, and the composition is formulated at a concentration suitable for direct administration to a subject in need thereof. Hochrainer *et al.* does not teach or suggest these compositions.

A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed subject matter. See, *e.g.*, *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). A *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. See, *e.g.*, *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

Hochrainer *et al.* teaches an "active substance concentrate" that must be diluted prior to administration to a subject in need thereof. The reference neither teaches nor suggests that the "pharmaceutical preparation" resulting

from dilution of the "active substance concentrate" is stable during long term storage. To the contrary, the reference teaches that:

> In the past it has been found that liquid aerosol formulations of formoterol are not suitable for use in inhalers intended for ambulatory inhalation treatment since *formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time*. (emphasis added)

Prior to Hochrainer

See, column 1, lines 30-35 of the reference.

Thus, Hochrainer *et al.* teaches away from the claimed subject matter. Therefore, the instant claims cannot be *prima facie* obvious over the teachings of Hochrainer *et al.*

The teachings of Bartow *et al.* and the PDR entry for FLOVENT® do not cure the defects in Hochrainer *et al.*

Bartow *et al.* and the PDR entry for FLOVENT® do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Neither Bartow *et al.* nor the PDR teach or suggest modification of the "active substance concentrate" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of the instant claims. Bartow *et al.* and the PDR do not teach or suggest modifying the "active substance concentrate" of Hochrainer *et al.* such that the composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof, as required by the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, the instant claims are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

The Office Action fails to set forth a *prima facie* case of obvi usn ss

In order to establish a *prima facie* case of obviousness, the cited references must provide a teaching or suggestion that would motivate one of ordinary skill in the art to do what applicant has done. Applicant respectfully submits that no such teaching or suggestion exists in the cited references. Hochrainer *et al.* teaches an "active substance concentrate" that must be diluted prior to administration to a subject in need thereof, and teaches away from the instantly-claimed pharmaceutical compositions. Bartow *et al.* and the PDR do not cure the defects of Hochrainer *et al.* Therefore, the instant claims are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

Applicant respectfully requests reconsideration and removal of this rejection.

Response to arguments

The Office Action alleges that the argument that the "Hochrainer *et al.* formulation is highly concentrated and cannot be directly administered to a patient in need thereof" is a mischaracterization of the reference since the reference allegedly teaches that its compositions can be administered (see, columns 4-5).

Hochrainer *et al.* does not teach or suggest pharmaceutical compositions that are stable for long term storage and are suitable for direct administration. The reference teaches an "active substance concentrate" that is stable for long term storage, but "according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation" (see, column 4, lines 9-11). The reference teaches that the "use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation)" (see, column 4, lines 11-13). Thus, the reference teaches that "pharmaceutical preparations" may be prepared from the "active substance concentrate" and subsequently administered to a subject in need thereof, but does not teach or

suggest that the "active substance concentrate" may be administered to a subject in need thereof.

Furthermore, the reference does not teach or suggest that the "pharmaceutical preparations" taught therein are stable during long term storage. As described in detail above, the reference teaches that liquid aerosol formulations of formoterol are not stable during long term storage. Thus, the reference actually teaches away from the claimed subject matter (see, column 1, lines 30-35 of the reference). Therefore, instant claims 1-64, 69-83, 87-89, 99-112 and 117-119 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

REJECTION OF CLAIM 93 UNDER 35 U.S.C. §103(a)

Claim 93 is rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2)*:303-322) and the PDR (Physician's Desk Reference) entry for FLOVENT® as applied to claims 1-64, 69-83, 87-89, 99-112 and 117-119, and further in view of the PDR entries for albuterol, accolate and Zyflo. Applicant respectfully traverses this rejection.

The relevant law

The relevant law is previously described.

The instant claims

Claim 93 is directed to the pharmaceutical composition of claim 1 as described above, further containing one or more of (a) to (j) as follows: (a) a β_2-adrenoreceptor agonist; (b) a dopamine (D_2) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lypoxygenase inhibitor; or (j) an anti-IgE antibody.

The teachings of Hochrainer *et al.*

The teachings of Hochrainer *et al.* are described above.

Th teachings f Bartow *et al.*, the PDR ntry for FLOVENT® and the PDR entries for albuterol, accolate and Zyflo do not cure the defects in Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT® and the PDR entries for albuterol, accolate and Zyflo do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. The PDR entries for albuterol, accolate and Zyflo teach that albuterol, accolate and Zyflo are all known to be effective in treating asthma.

Instant claim 93 is directed to a pharmaceutical composition of claim 1, further containing one or more of (a)-(j). Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow *et al.* nor the PDR entries cited above teach or suggest modification of the "active substance concentrate" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of instant claim 93. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claim 93 is not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

The Office Action fails to set forth a *prima facie* case of obviousness

In order to establish a *prima facie* case of obviousness, the cited references must provide a teaching or suggestion that would motivate one of ordinary skill in the art to do what applicant has done. Applicant respectfully submits that no such teaching or suggestion exists in the cited references. Hochrainer *et al.* teaches an "active substance concentrate" that must be diluted prior to administration to a subject in need thereof, and teaches away

from the instantly-claimed pharmaceutical compositions. Bartow *et al.* and the PDR do not cure the defects of Hochrainer *et al.* Therefore, the instant claims are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

Applicant respectfully requests reconsideration and removal of this rejection.

Response to arguments

The Office Action alleges that the argument that the "Hochrainer *et al.* formulation is highly concentrated and cannot be directly administered to a patient in need thereof" is a mischaracterization of the reference since the reference allegedly teaches that its compositions can be administered (see, columns 4-5).

Hochrainer *et al.* does not teach or suggest pharmaceutical compositions that are stable for long term storage and are suitable for direct administration. The reference teaches an "active substance concentrate" that is stable for long term storage, but "according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation" (see, column 4, lines 9-11). The reference teaches that the "use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation)" (see, column 4, lines 11-13). Thus, the reference teaches that "pharmaceutical preparations" may be prepared from the "active substance concentrate" and subsequently administered to a subject in need thereof, but does not teach or suggest that the "active substance concentrate" may be administered to a subject in need thereof.

Furthermore, the reference does not teach or suggest that the "pharmaceutical preparations" taught therein are stable during long term storage. As described in detail above, the reference teaches that liquid aerosol formulations of formoterol are not stable during long term storage. Thus, the reference actually teaches away from the claimed subject matter (see, column

1, lines 30-35 of the reference). Therefore, instant claim 93 is not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

REJECTION OF CLAIMS 113-115 (in so far as they read on ipratropium bromide) AND 116 UNDER 35 U.S.C. §103(a)

Claims 113-115 (in so far as they read on ipratropium bromide) and 116 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2)*:303-322) and the PDR (Physician's Desk Reference) entry for FLOVENT® as applied to claims 1-64, 69-83, 87-89, 99-112 and 117-119, and further in view of Hardman *et al.* (Goodman Gilman's, The Pharmacological Basis of Therapeutics, 1996, page 665). Applicant respectfully traverses this rejection.

The relevant law

The relevant law is previously described.

The instant claims

Claim 113 is directed to the pharmaceutical composition of claim 1 as described above, further containing an anticholinergic agent. Claims 114-116 further describe the anticholinergic agent of claim 113.

The teachings of Hochrainer *et al.*

The teachings of Hochrainer *et al.* are described above.

The teachings of Bartow *et al.*, the PDR entry for FLOVENT® and Hardman *et al.* do not cure the defects in Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT® and Hardman *et al.* do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Hardman *et al.* teaches that ipratropium bromide is an anticholinergic agent useful in treating asthma.

Instant claims 113-115 (in so far as they read on ipratropium bromide) and 116 are directed to a pharmaceutical composition of claim 1, further containing an anticholinergic agent. Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow *et al.*, the PDR nor Hardman *et al.* teach or suggest modification of the "active substance concentrate" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claims 113-115 (in so far as they read on ipratropium bromide) and 116 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Hardman *et al.*

The Office Action fails to set forth a *prima facie* case of obviousness

In order to establish a *prima facie* case of obviousness, the cited references must provide a teaching or suggestion that would motivate one of ordinary skill in the art to do what applicant has done. Applicant respectfully submits that no such teaching or suggestion exists in the cited references. Hochrainer *et al.* teaches an "active substance concentrate" that must be diluted prior to administration to a subject in need thereof, and teaches away from the instantly-claimed pharmaceutical compositions. Bartow *et al.*, the PDR and Hardman *et al.* do not cure the defects of Hochrainer *et al.* Therefore, the instant claims are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Hardman *et al.*

Applicant respectfully requests reconsideration and removal of this rejection.

R sponse to argum nts

The Office Action alleges that the argument that the "Hochrainer *et al.* formulation is highly concentrated and cannot be directly administered to a patient in need thereof" is a mischaracterization of the reference since the reference allegedly teaches that its compositions can be administered (see, columns 4-5).

Hochrainer *et al.* does not teach or suggest pharmaceutical compositions that are stable for long term storage and are suitable for direct administration. The reference teaches an "active substance concentrate" that is stable for long term storage, but "according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation" (see, column 4, lines 9-11). The reference teaches that the "use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation)" (see, column 4, lines 11-13). Thus, the reference teaches that "pharmaceutical preparations" may be prepared from the "active substance concentrate" and subsequently administered to a subject in need thereof, but does not teach or suggest that the "active substance concentrate" may be administered to a subject in need thereof.

Furthermore, the reference does not teach or suggest that the "pharmaceutical preparations" taught therein are stable during long term storage. As described in detail above, the reference teaches that liquid aerosol formulations of formoterol are not stable during long term storage. Thus, the reference actually teaches away from the claimed subject matter (see, column 1, lines 30-35 of the reference). Therefore, instant claims 113-115 (in so far as they read on ipratropium bromide) and 116 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Hardman *et al.*

REJECTION OF CLAIMS 113-115 (in s far as they r ad n tiotr pium bromid) AND 120-121 UNDER 35 U.S.C. §103(a)

Claims 113-115 (in so far as they read on tiotropium bromide) and 120-121 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2)*:303-322), the PDR (Physician's Desk Reference) entry for FLOVENT® as applied to claims 1-64, 69-83, 87-89, 99-112 and 117-119, and further in view of Leckie *et al.* (*Novel Therapy of COPD, abstract Jan. 2000*). Applicant respectfully traverses this rejection.

The relevant law

The relevant law is previously described.

The instant claims

Claim 113 is directed to the pharmaceutical composition of claim 1, further containing an anticholinergic agent. Claims 114-115 and 120-121 further describe the anticholinergic agent of claim 113.

The teachings of Hochrainer *et al.*

The teachings of Hochrainer *et al.* are described above.

The teachings of Bartow *et al.*, the PDR entry for FLOVENT® and Leckie *et al.* do not cure the defects in Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT®, and Leckie *et al.* do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Leckie *et al.* teaches that tiotropium bromide is a known bronchiodilator employed in treating asthma.

Instant claims 113-115 (in so far as they read on tiotropium bromide) and 120-121 are directed to a pharmaceutical composition of claim 1, further containing an anticholinergic agent. Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water,

and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow *et al.*, the PDR or Leckie *et al.* teach or suggest modification of the "liquid active substance concentrate" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions used in the methods of the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claims 113-115 (in so far as they read on tiotropium bromide) and 120-121 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Leckie *et al.*

The Office Action fails to set forth a *prima facie* case of obviousness

In order to establish a *prima facie* case of obviousness, the cited references must provide a teaching or suggestion that would motivate one of ordinary skill in the art to do what applicant has done. Applicant respectfully submits that no such teaching or suggestion exists in the cited references. Hochrainer *et al.* teaches an "active substance concentrate" that must be diluted prior to administration to a subject in need thereof, and teaches away from the instantly-claimed pharmaceutical compositions. Bartow *et al.*, the PDR and Leckie *et al.* do not cure the defects of Hochrainer *et al.* Therefore, the instant claims are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Leckie *et al.*

Applicant respectfully requests reconsideration and removal of this rejection.

Response to arguments

The Office Action alleges that the argument that the "Hochrainer *et al.* formulation is highly concentrated and cannot be directly administered to a patient in need thereof" is a mischaracterization of the reference since the reference allegedly teaches that its compositions can be administered (see, columns 4-5).

Hochrainer *et al.* does not teach or suggest pharmaceutical compositions that are stable for long term storage and are suitable for direct administration. The reference teaches an "active substance concentrate" that is stable for long term storage, but "according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation" (see, column 4, lines 9-11). The reference teaches that the "use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation)" (see, column 4, lines 11-13). Thus, the reference teaches that "pharmaceutical preparations" may be prepared from the "active substance concentrate" and subsequently administered to a subject in need thereof, but does not teach or suggest that the "active substance concentrate" may be administered to a subject in need thereof.

Furthermore, the reference does not teach or suggest that the "pharmaceutical preparations" taught therein are stable during long term storage. As described in detail above, the reference teaches that liquid aerosol formulations of formoterol are not stable during long term storage. Thus, the reference actually teaches away from the claimed subject matter (see, column 1, lines 30-35 of the reference). Therefore, instant claims 113-115 (in so far as they read on tiotropium bromide) and 120-121 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Leckie *et al.*

* * *

In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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